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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 03/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,182	BANKS, WILLIAM A.	
	Examiner	Art Unit	
	Daniel Kolker	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-76* is/are pending in the application.

4a) Of the above claim(s) *6-76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-76* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *30 August 2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response to the restriction requirement and accompanying remarks filed 1 March 2005 have been entered. Claims 1 – 76 are pending in the instant application.

Election/Restrictions

2. Applicant's election with traverse of Group I, claims 1 – 10, and election of epinephrine as the agent and SEQ ID NO:4 as the leptin in the reply filed on 1 March 2005 is acknowledged. The traversal is on the ground(s) that:

a) The restriction between Groups I – VI is improper.

b) Searching more than one leptin would not present a burden for the office, as several of the sequences are closely related.

It is noted that applicant did not traverse the requirement for election of a specific agent that modulates leptin transport.

This is found persuasive in part for the following reasons:

a) Applicant argues that the claims share a common technical feature. However, in order for there to be unity of invention, the various inventions must share a special technical feature, PCT Rule 13.2 defines as making a contribution over the prior art. The first stated technical feature is a method of modulating leptin transport across the blood-brain barrier, comprising the administration, to a mammal, of an effective amount of one or more compositions including adrenergic agonists, adrenergic antagonists, neurotransmitters, cytokines, amino acids, opiate peptides, purinergic agonists, glutaminergic agonists and metabolites thereof. This is not a contribution over the prior art for the reasons made of record in the restriction requirement mailed 1 February 2005 and reiterated here.

Greenway et al. (U.S. Patent 4,525,359) teaches the administration of isoproteronol and yohimbine to mammals. While Greenway did not explicitly measure transport of leptin across the blood-brain barrier, that is not a requirement of the method of claim 1. The only requirement is the administration of one of the agents listed in the preceding paragraph. The abstract of Greenway identifies isoproteronol as an adrenergic stimulator (i.e. agonist) and identifies yohimbine as an adrenergic inhibitor (i.e. antagonist). Furthermore, Gamaro et al. (1997. Neurobiology of Learning and Memory 68:221 – 229; note that a published erratum appears in Neurobiology of Learning and Memory 71:126, which is attached to the publication provided with this office action, and indicates that the units of epinephrine are ug/kg, not mg/kg as

originally appeared in the published paper.) teach a method of administering epinephrine by intraperiotneal injection at 625 ug/kg. It is acknowledged that neither Greenway nor Gamaro measured the transport of leptin across the blood-brain barrier. However, measuring such is not a requirement for the method. Clearly the administration of agonists or antagonists to adrenergic receptors, which is the only step of the method of claim 1, is not a contribution over the prior art. Therefore, it is not a special technical feature, and so there cannot be a special technical feature which links all inventions.

On p. 4 of the remarks filed 1 March 2005, applicant argues that because the international search report did not find the same lack of unity that the examiner found, the examiner should defer to the lack of unity objection made of record at the international phase. Applicant's arguments have been fully considered but not found persuasive. 35 U.S.C 372(b)(2) states that upon entry to the national stage of examination, the application is subject to re-examination for lack of unity. The restriction between Groups I – VI is maintained.

b) Applicant argues that the species of Group B, leptins, form a general inventive concept and therefore should be rejoined. This argument is not persuasive, as giving the claims their broadest reasonable interpretation necessitates including not only the peptide sequences enumerated in the sequence list, but also all analogs, variants, fusion proteins, and chemically modified derivatives. Furthermore, applicant indicates that SEQ ID NOs:4 and 6 are both human leptins, the difference being that one has the signal peptide and one is the mature protein and as such there would not be a serious burden on the examiner to search both sequences together. This reasoning is persuasive; both SEQ ID NO:4 and 6 will be examined in the instant office action.

The requirement is still deemed proper and is therefore made FINAL.

Claims 6 – 76 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and/or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 1 March 2005.

Claims 1 – 5 are under examination in the instant office action.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1 – 5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for increased transport of leptin across the blood-brain barrier (BBB) following intravenous or intraperitoneal administration of epinephrine, cirazoline, benoxathian, phentolamine, yohimbine, prasozin, adenosine, or glutamate, wherein leptin is either co-administered or not, does not reasonably provide enablement for increased transport of leptin across the BBB following administration by any other route of administration, or with any other compound, nor for co-administration of leptin variants, analogs, fusion proteins, derivates or fragments. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Utility is acknowledged because it is well-recognized in the art that increasing the transport of leptin across the BBB would be useful for decreasing obesity (see, for example Caro et al., 1996, Lancet 348:159 – 161; as well as Ramsey et al., (1998). Journal of Clinical Endocrinology and Metabolism 83:3230 – 3235, cited by applicant on the information disclosure statement), particularly p. 3234, middle of first complete paragraph.

The claims are drawn to modulating transport of leptin across the BBB via administration of any adrenergic agonist or antagonist, neurotransmitter, cytokine, amino acid, opiate peptide, purinergic agonist, glutaminergic agonist, or any metabolite of any of the above. The claims are sufficiently broad to include administration of any of the above-listed agents by any route, including those expressly enumerated in claim 2. The specification (p. 17 – 18) discloses that intraperitoneal administration of epinephrine increases the uptake of radio-labeled, intravenously administered leptin by the brain. Furthermore, the specification discloses the administration of tyrosine and phenylalanine in a similar method (p. 22 – 23) but indicates that while tyrosine is marginally effective phenylalanine is not effective. Similarly p. 24 indicates that argenine, phenylalanine, tryptophan, leucine, threonine, and leucine have no effect on transport of leptin across the BBB. The data presented on p. 25 indicate that while epinephrine is a neurotransmitter and is effective in modulating transport of leptin across the BBB when administered intravenously, neither epinephrine nor any other neurotransmitter administered by

applicant is effective when administered intracerebralventricularly (ICV). Furthermore no other neurotransmitter is effective when administered IV.

Furthermore, the specification indicates that adrenergic agonists in general are not effective in modulating the transport of leptin across the BBB. While ispoproterenol and arterenol are effective in this method, neither clonidine nor L-phenylephrine are effective (specification, p. 26). Adrenergic antagonists as a generic class are also not effective in modulating leptin transport across the BBB: phentolamine, yohimbine, and prasozin decrease leptin uptake, but D,L-propanolol does not modulate uptake. Additionally, while the alpha-1 adrenergic agonist cirazoline and the antagonist benoxathian modulate uptake, others listed in table 9 (p. 28) do not. The specification indicates that TNF-alpha does not modulate leptin uptake (p. 29). While TNF-alpha knockout mice show altered responses to leptin saturation (p. 29), this does not indicate that cytokines in general are effective modulators, or that TNF-alpha is even involved in leptin transport. In fact TNF-alpha induces production of the leptin protein (see Finck et al., American Journal of Phsyiology 278:R537-R543), so the data presented by applicant are not supportive of the conclusion that cytokines increase leptin transport across the BBB.

As mentioned previously, the specification discloses that while intravenous administration of epinephrine is effective in modulating leptin transport across the BBB, other routes of administration, including ICV administration, are not effective. Claim 2 explicitly recites ICV as one of the routes of administration, but it is clear that this will not work, as the specification discloses that ICV injection of epinephrine does not modulate transport of leptin across the BBB (p. 25, lines 9 – 18). Furthermore, claim 2 recites intracisternal injection, which is defined by Stedman's Medical Dictionary as a route that will allow injection into the ventricles. Because IT injection is synonymous with ICV injection clearly this is also not enabled.

Claims 3 and 4 are drawn to the co-administration of leptin, or variants, analogs, fusions, derivatives, or fragments thereof. The specification (p. 10 – 11) discloses particular substitutions and fragments which applicant has contemplated, and which appear to be preferred embodiments. It is noted that all working examples were performed with a single leptin, and there is no evidence that the fragments and fusion molecules disclosed in the specification in fact will be transported across the BBB. If, for example, one of the molecules listed on p. 11 binds to a leptin transporter but cannot be transported because it is missing a crucial moiety, then it would not in fact modulate transport of leptin across the BBB. Ramsey et

al. (cited on the information disclosure statement) teach that proteins which bind leptin may alter the transport of leptin across the BBB (p. 3234, first complete paragraph). This suggests that the moieties involved in leptin binding are crucial to the transport across the BBB. The post-filing teachings of Peelman et al. (2004. Journal of Biological Chemistry 279:41038-41046) indicate that single amino-acid changes in the sequence of mouse leptin can drastically alter one of its activities i.e. its ability to signal through its receptor (see Table 1 of Peelman), and can also change its binding properties (see Table 2). Interestingly, some mutations (for example, R20N) affect both properties whereas others (for example, Q75S) affect only binding and others (for example, S117Q) affect only signaling. Therefore, even four years after the international filing date, the art indicated that changes in leptin function cannot be easily predicted from changes in structure.

Claims 3 and 4 recite SEQ ID NOs which correspond to mouse and human leptin. The specification discloses that epinephrine, among certain other compounds, is able to increase the transport of leptin across the BBB. However, nowhere in the working examples is it stated which species of leptin is transported across the BBB. Mouse and human leptin are only 80.9% identical at the amino acid level, and the post-filing teachings of Peelman et al. indicate that subtle changes, even single amino acid substitutions, can influence leptin's biological activity. Given the unpredictability in the art, the sensitivity of leptin to subtle variations in sequence, and the relatively low homology between the human and mouse sequences, it is not clear that the methods will work with both human and mouse sequences, and it is less clear that the full scope of claims 3 and 4 (i.e. including variants, analogs, and fragments of leptin) are enabled.

The claims are sufficiently broad to include non-preferred fragments, including those that lack moieties essential for transport across the BBB or leptin action in neurons, as well as for fragments as small as a single amino acid. While guidance as to which fragments could be used are given in the specification, the claims are so broad that they encompass an unreasonable number of non-functional embodiments. Furthermore, the claims are drawn to methods of modulating leptin transport across the BBB, but only a signle embodiment (example 8) indicates that leptin transport can be decreased.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6)

breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

The nature of the invention, transport of peptides across the BBB, is complex. The claims are broad in that they are drawn to classes of molecules (i.e. adrenergic agonists and neurotransmitters). However the specification discloses either a single example of a class of molecules (i.e. adenosine is the only purinergic agonist) or multiple examples wherein only some are effective (e.g. many of the adrenergic agonists used on p. 28 of the specification are not effective in modulating leptin transport across the BBB). The claims are also broad in that they are drawn to routes of agents and administration which are known not to work, and to analogs and derivatives of leptin that are limited by neither structure nor by function. Clearly the level of predictability is low, and the claims are quite broad. It would require undue experimentation on the part of the skilled artisan to make and use the invention commensurate in scope with the claims.

5. Claims 1 – 5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to broad classes of agents that are not limited by structure. For example, claim 1 is drawn to neurotransmitters, which can be small molecules such as dopamine, single amino acids such as glutamate, or proteins such as neuropeptide Y. Similarly, the terms "agonists" and "antagonists" are functional, not structural definitions. Applicant has quite clearly disclosed five neurotransmitters (specification, p. 25), multiple adrenergic agonists and antagonists, all of which appear to be small organic molecules (specification, p. 26 – 28), as well as a single cytokine (TNF-alpha, p. 28-29). Furthermore applicant has disclosed specific leptins, some of which are identified by SEQ ID NO: (i.e. the mature protein and corresponding full-length protein with the signal sequence from both mouse and human), and others of which appear to be described in sufficient detail that one of skill in the art could make them (e.g. examples a – e on p. 11), although others such as "fragments" of leptin and "metabolites" of all agents do not meet the written description requirement. The claims do not recite which parts of

the sequence can be varied, which can be deleted, where insertions can be made, or even which parts of the sequence must be present for the molecule to be considered "leptin". The instant disclosure of a handful of molecules, however, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 2, and 5 are rejected under 35 U.S.C. 102(b) as being anticipated Gamaro et al. (1997. Neurobiology of Learning and Memory 68:221 – 229). Note that a published erratum appears in Neurobiology of Learning and Memory 71:126, which is attached to the publication provided with this office action, and indicates that the units of epinephrine are ug/kg, not mg/kg as originally appeared in the published paper. The claims are drawn to methods of increasing leptin transport across the BBB by administering epinephrine. The instant specification

discloses epinephrine was effective in modulating leptin transport across the BBB when given at doses (p. 29) that from 13.3 – 66 ug to mice weighing 17 – 22 g (p. 17). This corresponds to a dose of between 605 ug – 3882 ug / kg. Gamaro et al. administered epinephrine by intraperitoneal injection at 625 ug/kg (p. 223, first complete paragraph). This dose is effective in modulating the transport of leptin across the BBB, as disclosed in the instant specification. The preamble of claim 1 recites "a method for modulating transport of leptin" but the intended use is given no patentable weight; see MPEP 2111.02. The only requirement listed in the body of the claim is that the amount of the agent be effective. As noted in this paragraph, the guidance in the specification indicates that doses of epinephrine between 605 and 3882 ug / kg are effective amount of epinephrine. Since Gamaro et al. administered an amount of epinephrine within this range, the prior art teachings of Gamaro et al. anticipate claims 1, 2, and 5.

8. Claims 1, 2, and 5 rejected under 35 U.S.C. 102(a) as being anticipated by Mostyn et al. (reference C25 on the information disclosure statement filed 30 August 2002). Mostyn et al. teach a method of administering adrenaline to mice, at a dose of 1000 ug/kg (second paragraph). Adrenaline is a synonym of epinephrine. As noted in the previous paragraph, the specification clearly discloses which doses of epinephrine are effective in modulating the transport of leptin. The dose administered by Mostyn et al., 1000 ug/kg, is within the range of effective amounts. Furthermore Mostyn et al. teach that epinephrine decreases the amount of circulating leptin by 76% (see third paragraph), which is consistent with an increase in transport across the BBB. Since all mammals have leptin, the administration of epiniephrine is inherently sufficient to increase leptin transport across the BBB, independent of whether said transport was measured or not, as long as the dose is within the effective range. Applicant is advised that the publication date of this reference is March 1999, as evidenced by the enclosed printout from the publisher's website, and that the reference is an abstract presented at a meeting 30 September – 2 October 1998.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1 - 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gamaro et al. in view of Bigsby (U.S. Patent 3,074,847, issued 22 January 1963) and Banks et al. (reference C5 on the information disclosure statement). As detailed above, the preamble of the claim is not given patentable weight; see MPEP 2111.02. The claims are drawn to the administration of epinephrine and leptin. Gamaro et al. teach administration of epinephrine in a dose that is sufficient to modulate the transport of epinephrine across the BBB, as detailed in paragraph 7 above. Gamaro does not teach that epinephrine inhibits appetite.

Bigsby teaches that sympathomimetic drugs, including epinephrine, curb the appetite (column 1, lines 11 – 12, and column 2, lines 28 – 30). Neither Bigsby nor Gamaro teach administration of leptin.

Banks et al. teach a method of administering leptin to an mammal. Banks teaches that leptin suppresses food intake (second paragraph on p. 305).

It would have been obvious to one of ordinary skill in the art to co-administer epinephrine and leptin, with a reasonable expectation of success. Both leptin and epinephrine are appetite-suppressing compounds, and MPEP 2144.06 states that it is *prima facie* obvious to combine two compositions that have the same effect for the same purpose. Here, the purpose is to curb appetite. As the preamble of claim 1 is not limiting, and the bodies of the claims do not rely on the preamble for completeness, the administration of the two compounds together is sufficient to meet the limitations of the claims. The effects of the compounds are intrinsic properties which had been disclosed in the prior art.

Conclusion

11. No claim is allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on (571) 272-0829. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel E. Kolker, Ph.D.
March 29, 2005

SHARON TURNER, PH.D.
PRIMARY EXAMINER
3-30-05